SUPPLEMENTAL MATERIAL

Study Protocol

Methods for the literature search, data extraction, and analysis were specified in advance as outlined below:

Inclusion criteria

Studies meeting all of the following criteria were included:

1. Published studies irrespective of date of publication
2. Availability in the English language
3. Human subjects
4. Randomized control trial design
5. Clinical follow-up of any duration (including all-cause mortality, reinfarction, revascularization, cardiovascular (CV) mortality, need for repeat PCI, need for repeat coronary artery bypass grafting (CABG), stroke, contrast induced nephropathy (CIN) and major bleeding)

Exclusion criteria

Studies will be excluded if any of the following criteria are met:

1. Non-English language manuscripts
2. Studies without any clinical outcomes or control groups
3. Studies in animals
4. Imaging studies
5. Case reports, editorials, comments, letters, review articles, guidelines, or Non STEMI trials were also excluded from the analysis.

Systematic literature search

An electronic search of SCOPUS was performed in May 2015 for relevant randomized clinical trials. References of identified studies were manually searched for relevant publications. The search was independently implemented by two study investigators (NSB, PA) and verified by a third investigator (RK). The following search strategy was employed:

(TITLE-ABS-KEY("STEMI") OR TITLE-ABS-KEY("ST elevation myocardial infarction") OR TITLE-ABS-KEY("Acute myocardial infarction") AND TITLE-ABS-KEY("PCI") OR TITLE-ABS-KEY("Percutaneous coronary intervention") OR TITLE-ABS-KEY("angioplasty") AND TITLE-ABS-KEY("Culprit") OR TITLE-ABS-KEY("non-culprit") OR TITLE-ABS-KEY("complete revascularization")) AND (EXCLUDE(DOCTYPE, "re") OR EXCLUDE(DOCTYPE, "no") OR EXCLUDE(DOCTYPE, "ed") OR EXCLUDE(DOCTYPE, "le") OR EXCLUDE(DOCTYPE, "Undefined"))

Data selection and endpoints

The primary objective of this analysis was to evaluate the impact of various revascularization strategies versus the current standard, which is target/ culprit lesion revascularization, in patients presenting with ST-Elevation Myocardial Infarction. Data extracted from each trial included: 1) study details, including year, location, country, numbers of centers involved, duration of follow-up, number of patients, proportion of male patients, number of procedures, angiographic data, type of catheter-based therapy; 2) mortality outcomes, including all-cause, cardiovascular and non-cardiovascular mortality at end of reported follow up; 3) hemodynamic outcomes including technical success, presence of hemodynamic instability both before and after catheter-based

interventions, presence and improvement of left ventricular dysfunction, and occurrence of cardiac arrest prior to catheter-based intervention and peri-procedural and post-procedural cardiac arrest, 4) safety outcomes including minor and major access site bleeding, hemoptysis, bleeding at other sites, and intracranial bleeding. Multiple investigators performed data extraction (NSB, PA, RK). All investigators involved in data extraction (NSB, PA, RK) also checked for consistency before full-scale data extraction was carried out. All discrepancies in data extraction were resolved by mutual consensus.

Statistical analysis

After the data elements were verified for accuracy, systematic and statistical analyses were conducted using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey) and STATA, version 14.0 (StataCorp LP), respectively. We used random effects modeling for all analyses. We assessed for heterogeneity using the I^2 test (I^2 >50% with p-value < 0.05 considered as evidence of significant heterogeneity). We also performed a pre-specified sub-group analysis to assess the role of Fractional flow reserve (FFR) in patients undergoing complete revascularization (CR). Publication bias for the primary outcome was assessed using the funnel plot and Eggers regression method and was considered significant if the one tailed p-value was < 0.05. If significant publication bias was present, corrected estimates were calculated using the Duval and Tweedie trim and fill method. The analysis was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.

Table S1: Definitions

In all instances, the authors' definition of the below mentioned characteristics was used. Where the definition has evolved since the time of publication or there were multiple interpretations, we used the following definitions:

Follow-up	Follow-up was measured in patients per 100 person years. This number was derived by multiplying the mean or median follow-up in months (as stated by authors) by the numbers of patients and then dividing by 12.
Number of procedures	Defined as being the same as the number of patients unless stated otherwise by the authors.
Multi-vessel coronary artery disease	Flow limiting coronary artery disease in $\geq$ 1 non-culprit epicardial coronary artery as defined by authors or > 50% obstruction by angiogram or Fractional Flow Reserve (FFR) < 0.8 in staged left heart catheterization.
ST-elevation myocardial infarction	As defined by authors or ACC/AHA/SCAI or ESC consensus statement [1,2].
Hemodynamic instability	Defined as patients with a systolic blood pressure less than 90 mmHg, a systolic blood pressure drop greater than 40mmHg drop for 15 minutes or more, or exhibiting a requirement for inotropic or vasopressor support. Shock index $\geq$1 was also used to define hemodynamic instability where the authors stated individual patients' heart rate and blood pressure readings. Additionally, any patients described as being hemodynamically unstable by the authors (without a definition) and patients who had experienced cardiac arrest immediately prior to the procedure were also defined as being hemodynamically unstable.
Complete revascularization	Revascularization of the culprit artery and all flow-limiting epicardial coronary arteries.
Staged revascularization	Revascularization of the culprit artery with later elective revascularization of all flow-limiting epicardial coronary arteries.
Culprit lesion revascularization	Revascularization of culprit artery only.
Re-infarction	As defined by ACC/AHA/SCAI guidelines or as defined by authors [1,2].
In-stent thrombosis	Defined as either angiographically confirmed partial or complete occlusion of stent or repeat myocardial infarction in the distribution of the revascularized vessel.

All-cause mortality	All deaths till the end of the follow-up period after being discharged from the index hospitalization. Where follow-up beyond discharge was not reported, this was the same as survival to discharge. The cause of death was further sub-divided into cardiovascular mortality and non-cardiovascular mortality. Where the cause of death could not be defined, the death was counted towards all-cause mortality without being included in the 'cardiovascular mortality' or 'non-cardiovascular mortality' sub-groups.
Major adverse cardiac event (MACE)	Due to the heterogeneity in definitions amongst the included trials we defined MACE as follows: mortality including all-cause death, any new myocardial infarction (fatal and non-fatal myocardial infarctions), and revascularization with either percutaneous coronary intervention or coronary artery bypass grafting.
Cardiovascular mortality	Death due to ventricular failure, myocardial infarction, or cardiac arrest till the end of the follow-up period.
Non-cardiovascular mortality	Death from all causes aside from those listed in 'cardiovascular mortality'.
Major bleeding	Major bleeding was defined as follows: major visceral bleeding as defined by authors (including intracranial hemorrhage); any bleeding requiring operative intervention or transfusion of at least two units of packed red blood cells; bleeding leading to shock as defined above.
Minor bleeding	Any other bleeding event that was not considered major bleeding.
Contrast-induced nephropathy (CIN)	Defined as the worsening of renal function after administration of radioactive contrast material. Per SCAI guidelines, CIN was defined as increase in serum baseline creatinine over 48 hours by >25% or an absolute increase of 0.25-0.5 mg/dl.[1,2]
Stroke	Any new focal neurologic deficit of suspected vascular origin persisting beyond 24 hours or as defined by authors.

Table S2: PRISMA checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6-8 and Appendix Section 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8 and Appendix Section 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-8 and 6-8 and Appendix Section 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-8 and Appendix Section 1

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-8 and Appendix Section 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-8 and Appendix Section 1
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8 and Appendix Section 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-8 and Appendix Section 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-8 and Appendix Section 1
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-8 and Appendix Section 1
Section/Topic	#	Checklist Item	Reported on Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8 and Appendix Section 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-8 and Appendix Section 1
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-12
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-8 and Appendix setion1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9 and 12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table S3: Outcomes reported in randomized clinical trials

Study	MACE Definition	CV mortality	All-cause Mortality	In-hospital death	Non-Fatal MI	MI	Reinfarction	Refractory Angina	Repeat Revascularization	PTCA or CABG	PTCA	CABG	Rehospitalization for ACS	CIN	Stroke	Major Bleeding
CvLPRIT/ Gershlick et al (3)	All-cause mortality, recurrent MI, HF, and repeat revascularization	*	*	NR	NR	*	*	NR	*	NR	NR	NR	NR	*	*	*
DANAMI3-PRIMULTI/ Engstrom et al (4)	All-cause mortality, non-fatal MI and ischemia-driven revascularization	*	*	NR	*	NR	NR	NR	*	Calculated	*	Calculated	NR	*	*	*
Tarasov et al (5)	CV mortality, MI, target vessel revascularization	*	*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
PRAMI/ Wald et al (6)	As above	*	*	NR	*	NR	NR	*	*	*	NR	NR	NR	*	*	*
Dambrink et al (7)	All-cause mortality, non-fatal MI, and additional unplanned revascularization	NR	Calculated	NR	NR	*	NR	NR	*	*	*	*	NR	NR	NR	NR
Politi et al (8)	All-cause mortality, in-hospital mortality, reinfarction, rehospitalization for ACS, repeat revascularization	*	*	*	NR	NR	*	NR	*	*	*	*	*	*	NR	NR
HELP-AMI/ Di Mario et al (9)	Not defined but reported	NR	*	*	NR	*	NR	NR	NR	*	NR	NR	NR	NR	NR	NR
PRIMA/ Ochala et al (10)	All-cause mortality, repeat MI, target vessel revascularization	*	*	NR	NR	NR	*	NR	*	Calculated	*	*	NR	NR	NR	*

MACE: Major Adverse Cardiovascular Events; MI: Myocardial infarction; NR: Not reported; CV: Cardiovascular; PTCA: Percutaneous Transluminal Coronary Angioplasty; CABG: Coronary Artery Bypass Grafting; ACS: Acute Coronary Syndrome; CIN: Contrast-induced Nephropathy; CvLPRIT: Randomized Trial of

Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease; PRAMI: Randomized Trial of Preventive Angioplasty in Myocardial Infarction; HELP-AMI: Single vs. multivessel treatment during primary angioplasty: results of the multicenter randomized HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction; DANAMI3-PRIMULTI: The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction PRImary PCI in MULTIvessel Disease; PRIMA: PRIMAry percutaneous intervention in acute myocardial infarction.

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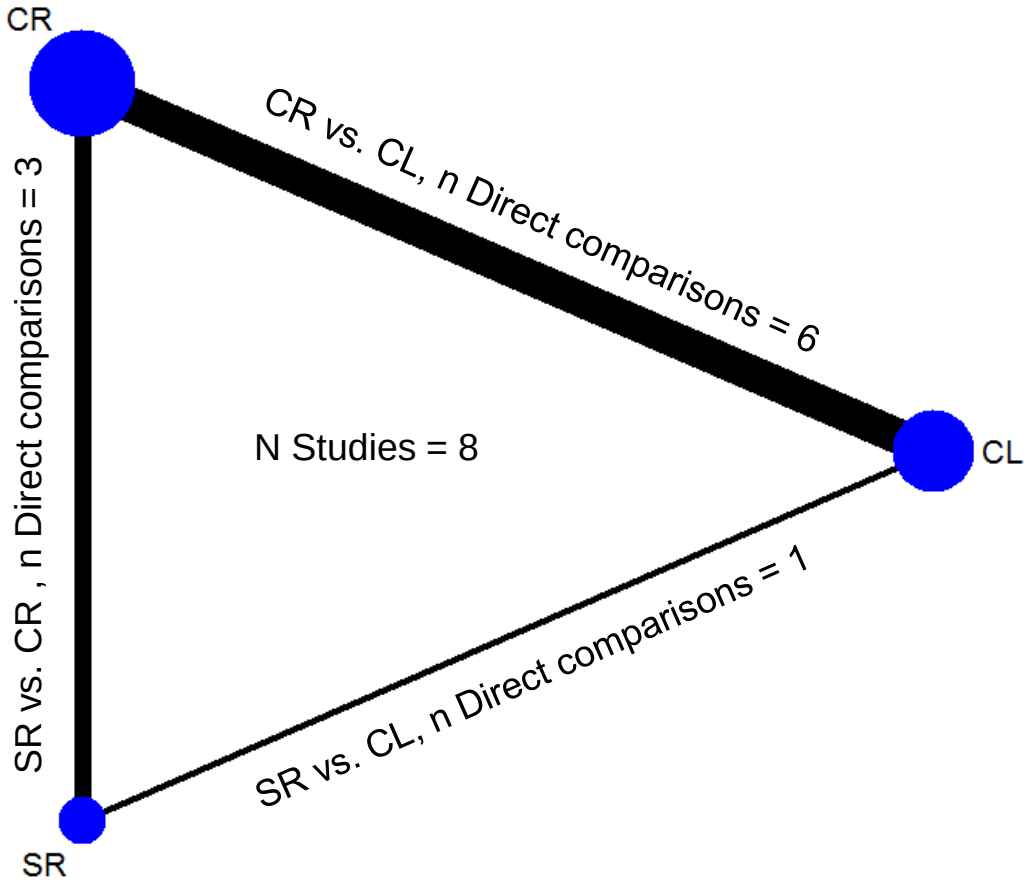

Figure S1: Network for treatment comparison for primary outcome.
The solid blue circle represents the treatment. The size of the circle corresponds to the total sample size of treatment from all included trials. The solid black line represents direct treatment comparisons. The thickness of line corresponds to total sample size assessing the comparison.

CR = complete revascularization at index angiogram; SR = staged revascularization of non-culprit vessels after culprit lesion revascularization at index angiogram; CL = culprit lesion revascularization only at index angiogram.

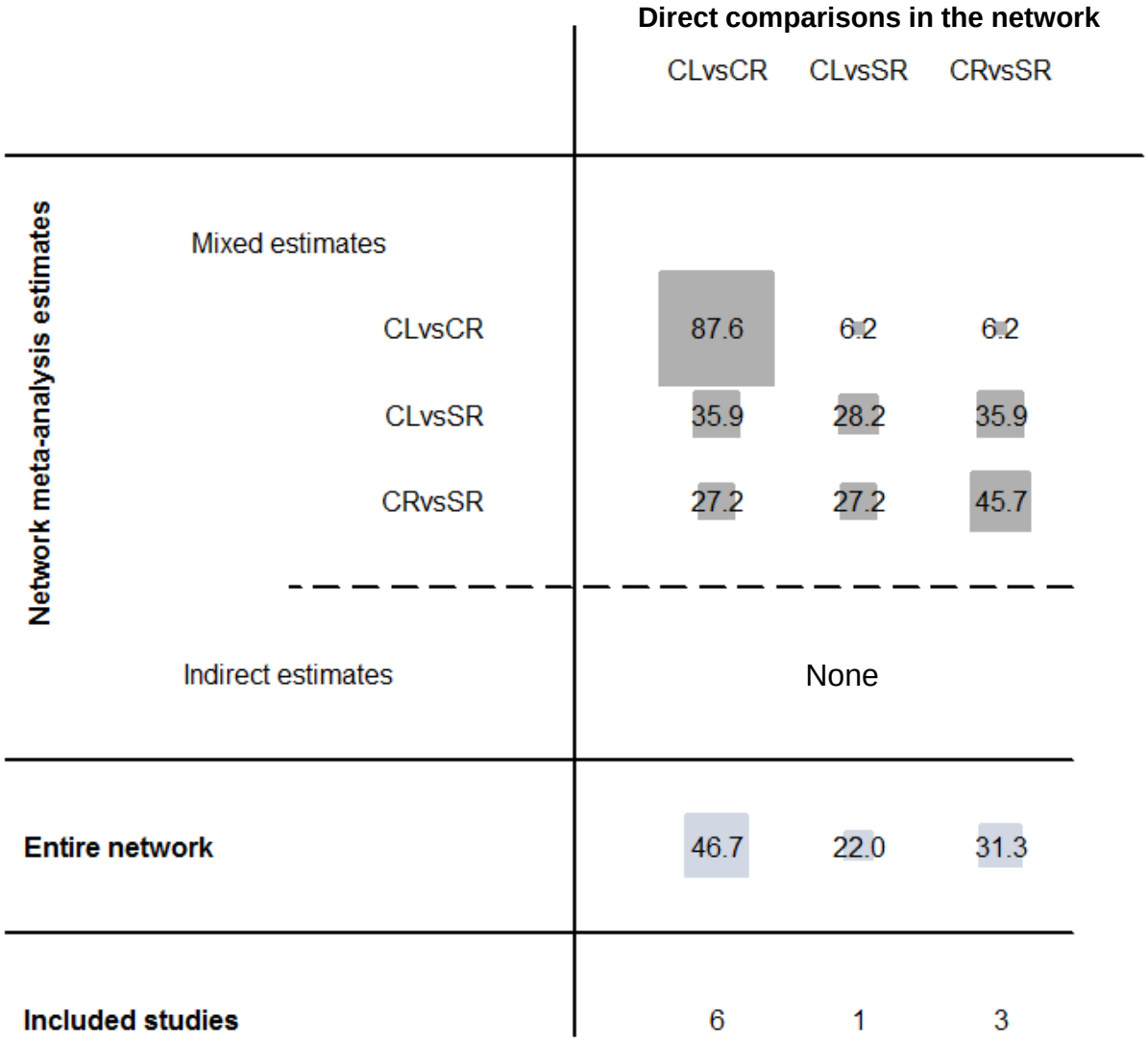

Figure S2: Contribution plot for revascularization strategy in ST-elevation myocardial infarction network.
The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effects (vertical axis). The numbers re-express the weights as percentages.

CR = complete revascularization at index angiogram; SR = staged revascularization of non-culprit vessels after culprit lesion revascularization at index angiogram; CL = culprit lesion revascularization only at index angiogram.

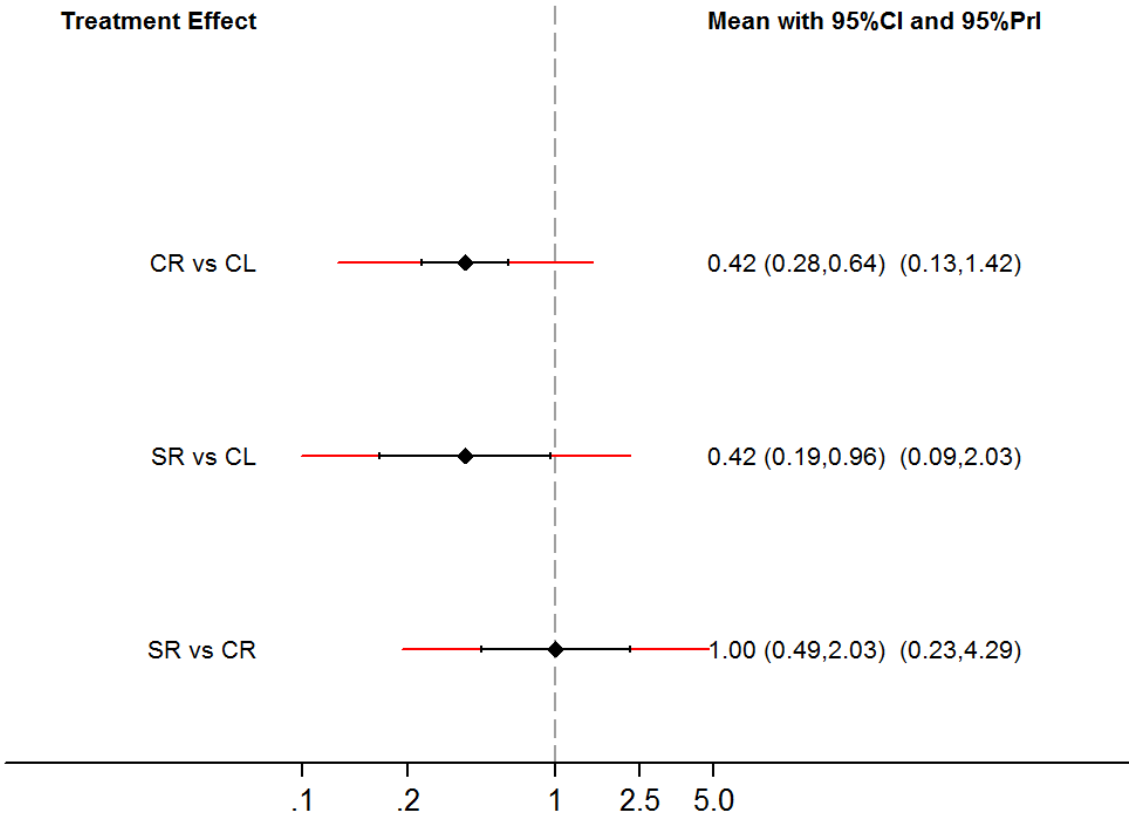

Figure S3: Predictive interval plot on a logarithmic scale.
The black solid lines represent the confidence intervals for summary odds ratios for each comparison and the red dashed lines the respective predictive intervals. The blue line is the line of no effect (odds ratio equal to 1).

CR = complete revascularization at index angiogram; SR = staged revascularization of non-culprit vessels after culprit lesion revascularization ay index angiogram; CL = culprit lesion revascularization only at index angiogram

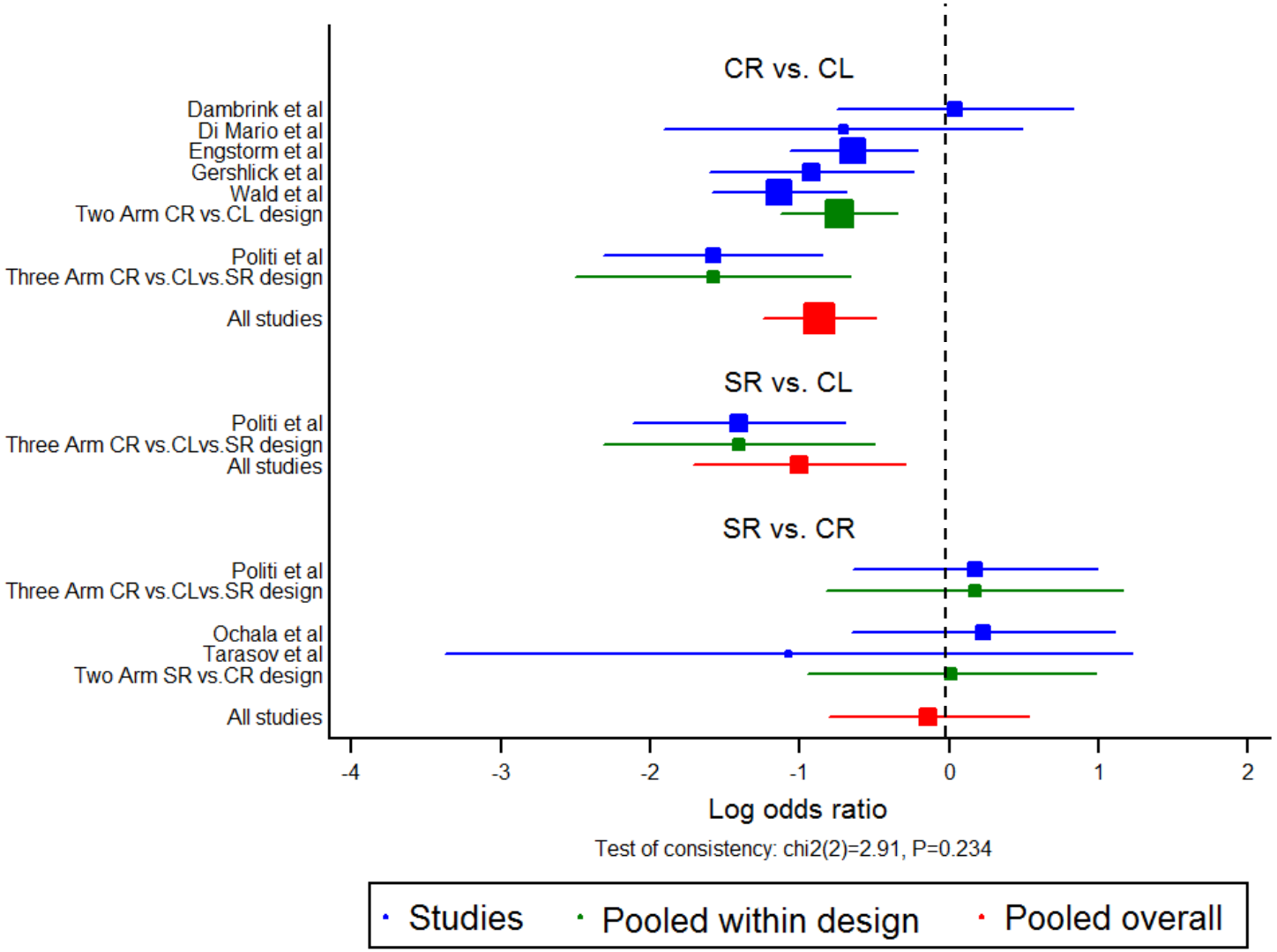

Figure S4: Network Forest plot on a logarithmic scale.
The blue solid lines represent the confidence intervals for log odds ratios for each comparison in individual studies and the green solid lines represents log odds ratio within study design and blue solid line represents respective overall log odds ratio using consistency and inconsistency models. The black dashed line is no effect (odds ratio equal to 1).

CR = complete revascularization at index angiogram; SR = staged revascularization of non-culprit vessels after culprit lesion revascularization ay index angiogram; CL = culprit lesion revascularization only at index angiogram

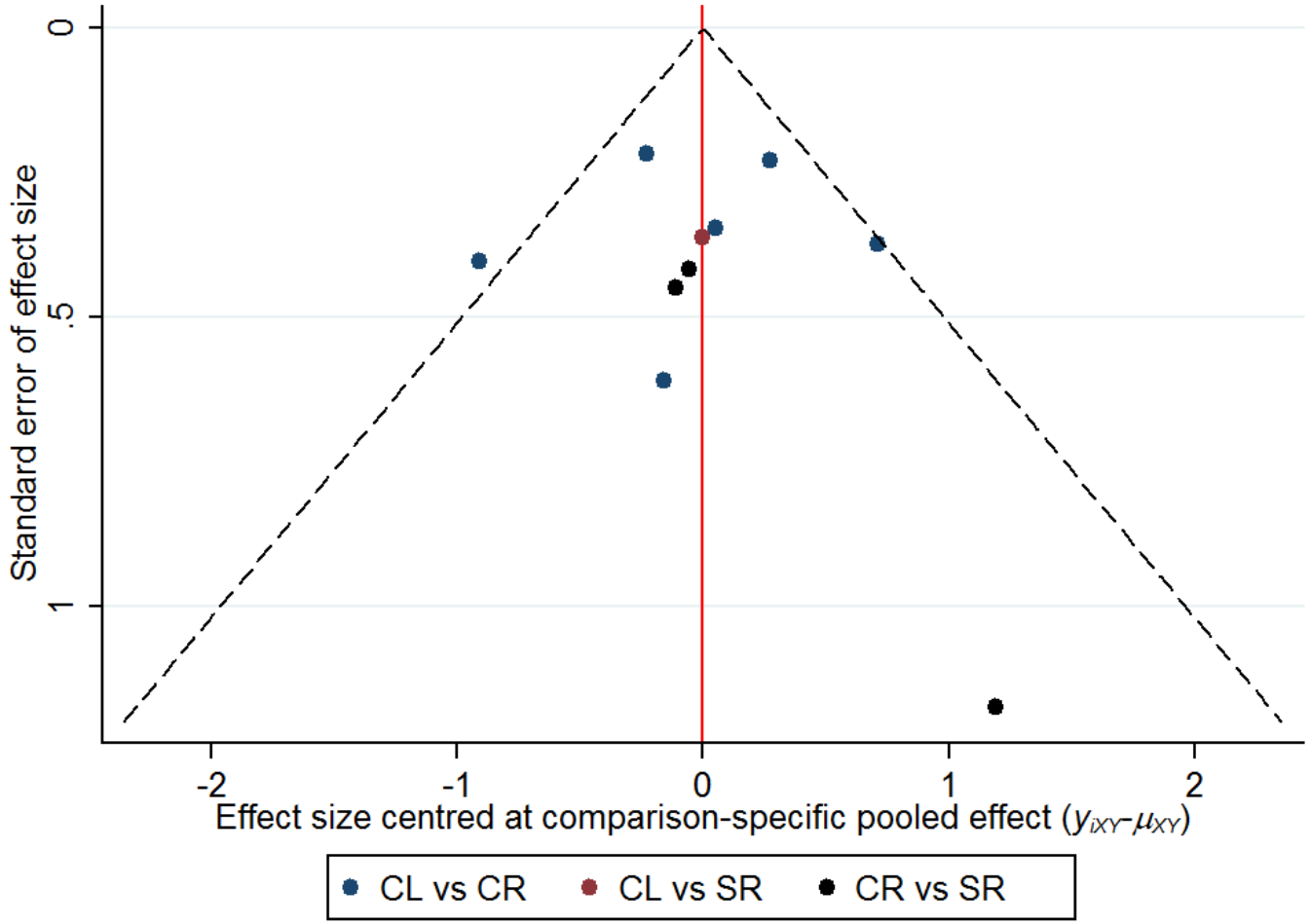

Figure S5: Comparison-adjusted funnel plot.
The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. Different colors correspond to different comparisons.

CR = complete revascularization at index angiogram; SR = staged revascularization of non-culprit vessels after culprit lesion revascularization ay index angiogram; CL = culprit lesion revascularization only at index angiogram